Current Status of Phase I Clinical Trials in Asia: an Academic Perspectives

Melva Louisa¹, Masahiro Takeuchi², Rianto Setiabudy¹, Nafrialdi¹, Madoka Takeuchi²

¹ Department of Pharmacology and Therapeutics, Faculty of Medicine, University of Indonesia. Jl. Salemba Raya no. 6, Jakarta Pusat 10430, Indonesia. Correspondence mail: melva.louisa@gmail.com.
² Department of Biostatistics and Clinical Medicine, Kitasato University, Japan.

ABSTRACT

Clinical trials increasingly occurred in Asia during the past years as pharmaceutical industries embraced globalization in the clinical research fields. The trend is true with phase III clinical trials but not for early stage/phase I clinical trials in Asian countries is still under-represented. The conduct of phase I clinical trials is considered more sophisticated and difficult than the later stage clinical trials. There are continuing concerns from the pharmaceutical industries about the capacity of Asian countries in conducting this type of clinical trials.

We highlighted several problems concerning the ethical and scientific issues, the implementation of ICH-GCP (International Harmonization - Good Clinical Practice) serta regulasi lokal, peneliti serta subjek uji klinik. Tujuan dari tulisan ini adalah memberikan pandangan mengenai kemampuan negara-negara Asia dalam melakukan uji klinik fase awal.

Kami menyoroti berbagai permasalahan dalam hal etik dan ilmiah, implementasi ICH-GCP serta regulasi lokal, peneliti serta subjek uji klinik. Tujuan dari tulisan ini adalah memberikan pandangan mengenai kemampuan negara-negara Asia dalam melakukan uji klinik fase awal.

Kata kuncii: fase I, uji klinik, Asia.

INTRODUCTION

As global simultaneous trials become a common strategy in drug development for multinational pharmaceutical companies, Asian countries has become important regions in conducting clinical trials. As clinical trials increasingly occur on a global scale, industry and government sponsors in wealthy countries move trials to less wealthy countries. The trend is true with phase III clinical trials, but not for the earlier stage of clinical trials. This phenomenon raises important questions about the opportunities and
challenges of early stage clinical trials in Asia. What is the Asian potential to conduct the phase I clinical trials? Why do the pharmaceutical industries have not given enough confidence to conduct the earlier trials in Asia? What are the roles of academia in this matter?

In this article, we discuss the trends of globalization of clinical trials, the involvement of Asian countries, and the opportunities, challenges and future directions in improving Asian capacity in conducting early stage drug trials.

TRENDS IN GLOBALIZATION OF CLINICAL RESEARCH

The world now has become more interdependent in the movement of free trade and global markets. Globalization has contributed to fundamental changes within the biomedical changes endeavor. Industry-sponsored clinical research has traditionally been carried out in relatively wealthy locations in America and Western Europe. However, in recent years, a shift has been observed to the less wealthy countries such as Eastern Europe, Latin America and Asian countries. Since 2002, the number of active Food and Drug Administration (FDA) – regulated investigators based outside the United States has grown by 15% annually, whereas the number of US-based investigators has declined by 5.5%.

Previous data showed one third of the industry-sponsored phase 3 clinical trials are being conducted solely outside the United States. But this trend is not true with first in human/phase I clinical trials.

To further explore this trend, we used the ClinicalTrials.gov registry to examine recruitment in industry-sponsored phase I interventional clinical trials from early 2007 to 2009. We found only 6.8% (319 out of 4665 studies) were conducted in Asian countries and that the majority of the studies were done by the Japan, Korea, India, Singapore and China. The top 3 countries that did the most of the phase I clinical trials were US, Canada and UK, hosting 64% of all clinical trial sites (US hosted 51%).

We also examine the trends for Asian countries involvement in phase III clinical trials since 2007, and found that considerably large percentage of the trials were done in Asian countries (1186 out of 4144 trials or 28.8%), while the US hosted 46.6% of phase III clinical trials.

Asia is the largest and most populous continent with approximately 4 billion people (60% of the world population). Yet, it is highly under-represented in the earlier phases of clinical drug trials, or rather an exclusion in the phase I clinical trials.

In Asia, Japan conducts most of the phase I trials (126 out of 319 trials). Japan alone accounts for about 10 per cent of the world’s pharmaceutical market, the second biggest national drug market next to USA.

Japan, Korea and China, although individually capable of growth, made a tripartite partnership as to address serious challenges in the global economy. These three countries recognized that each country is similar to each other. It is necessary for ethnic similarity to be shown for mutual utilization of clinical trial data. Still, the number of trials conducted in East Asia is relatively small.

In South Asia, India is the only country listed in the clinical trials registry. Despite having a huge population (of over 1 billion inhabitants), human resources and the country’s ambition to attract multinational pharmaceutical companies to conduct clinical trials in India, the country is still under-represented in phase I clinical trials. Actually, India is a particularly attractive site for such trials since there are people who have not been exposed to many medications but have myriad diseases, ranging from tropical infections to degenerative disorders. Virtually, all Indian doctors speak English, and many have acquired postgraduate qualifications abroad, primarily Britain or the United States. Added to these attractions are cheap labor and low infrastructure costs, which can reduce expenditures for clinical trials by as much as 60 percent. However, even from the viewpoint of the industry, there are some major drawbacks to working in India. Sponsors do not have exclusive rights to the clinical data they generate: because clinical trial reports are
In the public domain, manufacturers of generic drugs can use the data to obtain regulatory approval of their own versions of a drug.\textsuperscript{14}

South East Asia has been frequently set aside in clinical trials. Only Singapore, a small country with 4 million people plays a significant role in conducting phase I clinical trials. Singapore has been known for its friendly clinical trial environment. The country has built its infrastructure in clinical trials since 1978 with reference to the internationally accepted International Conference of Harmonization (ICH) Guideline for GCP.\textsuperscript{15} Indonesia, a country with almost 230 million inhabitants was not listed in the registry. Among other South East Asian countries, Indonesia has not been regarded as a

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\caption{Industry-sponsored phase I interventional clinical trials from 2007 to 2009. A. Worldwide; B. Asia}
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workable medical sites.\textsuperscript{16}

**THE OPPORTUNITIES AND CHALLENGES OF PHASE I CLINICAL TRIALS IN ASIA**

There are many benefits to conducting clinical trials in Asia. One of the major advantages includes lower trial cost per patient compared to the US and EU. Clinical trials in Asia also provide wider coverage of ethnic populations and extensive patients.\textsuperscript{17} Clinical trial capabilities in some Asian countries such as Japan, Korea and Singapore have improved to the point that there is simply no reason to maintain a bias in favor of US or Europe.\textsuperscript{3,18}

Conducting trials in Asian countries might also be justified if the research might address an important health problem in some specific countries such as infectious diseases, or represent a joint effort by the country sponsoring or conducting the study and the host country to address an important health problem in both countries.\textsuperscript{17} Due to the changes in living standards many diseases in Europe and US (eg. hypertension, diabetes) are now global diseases.\textsuperscript{19,20}

It is essential to conduct the clinical research in populations proportional to the potential uses of the products after approval, even from the earliest drug development process.\textsuperscript{17} Clinical trials of dengue vaccine listed in clinical trials are done mostly in the US (19 out of 31 trials), while it is widely known that the dengue fever and dengue hemorrhagic fever mostly spread in South East Asia.\textsuperscript{21} The same case also happens with phase I clinical trials of HIV/AIDS medicines, which is done in the US (721 of 875 studies). However, 90\% of the world’s 40 million people with HIV infection or AIDS live in developing countries.\textsuperscript{22}

Another justification of doing early clinical trials in Asia is that race and genetic factors may play pivotal parts in the variability of subjects’ responses to a medication and adverse drug reactions.\textsuperscript{23,24} Many adverse drug reactions arise because of genetic differences in drug metabolism, receptors, transporters, ion channels and other drug targets.\textsuperscript{25} Unfortunately, most clinical trials are not designed to deal with these issues, so the population involved in the study rarely mirrors the full spectrum of patients who are likely to receive the treatment.\textsuperscript{23}

Many challenges still need to be addressed. We highlighted several problems concerning the ethical and scientific issues, the implementation of ICH-GCP and local regulation, investigators and clinical trial subjects.

**Ethical and Scientific Issues**

The globalization of clinical trials has raised many ethical and scientific concerns. Many pharmaceutical companies judged that many Asian countries, mostly in South East Asian countries know little about conducting and quality of research with relatively little clinical research experiences.\textsuperscript{3}

It is true that phase I clinical trials requires a range of skill and expertise of the highest standard. Confidence in the results depends upon the clarity and understanding of the questions asked, and upon the quality of the trial design to answer them. However, the safety and well-being of the subjects, whether they be healthy individuals or patients – must always be a priority.\textsuperscript{8} After the TGN1412 incident in March 2006, where six trial subjects became seriously ill and were admitted to intensive care, the Medicines and Healthcare products Regulatory Agency (MHRA) has made a program of accreditation for first in human trial.\textsuperscript{26} The fact that many potential research centers in Asian countries have not been awarded with this certification keeps the industry from conducting first in human trials outside Europe or US.

There is also a major concern from the research community that the transfer of clinical research outside of US and Europe is done only to reduce cost and constraints of regulations that may be favourable to the industry’s implementation, but not out of the need to explore the safety and pharmacology of the drug in question to certain ethnic groups.\textsuperscript{27,28} Some studies have exploited the unfortunate conditions in which some people live as a result of economic and cultural factors beyond their control – factors that make them vulnerable and convenient for study.\textsuperscript{29}

Health care infrastructure is not working very well in some Asian countries. It is considered to be unethical for the intervention to be tested in host country where the intervention is not affordable. It is also unethical if the health care infrastructure cannot support proper distribution and usage, not allowing patients of any of its potential benefits.\textsuperscript{27}
The Implementation of GCP and Local Regulation

Most Asian countries now have implemented the International Conference on Harmonization – Good Clinical Practice (ICH-GCP) guidelines. Each country makes their own modifications according to the conditions of the countries.

Many of the regulatory bodies in Asia are not as constraint as the US or European countries. But then, some of the regulatory bodies in several countries have signed into many bureaucratic practices that are expensive, unnecessary and have applied them indiscriminately to all kinds of clinical trials. Sometimes, counterproductive regulations are made such as the prohibition of biological samples shipment out of the country, which in global trials are mandatory to have a central laboratory to reduce the deviation of results due to laboratory differences.

There are also concerns that many regulatory bodies are understaffed and lack the expertise to evaluate protocols. These often result in uncertainties or longer timelines in the clinical trial application approval. Regulatory approval in China for clinical trial initiation may take up nine months as the approvals dossier navigates its path through six regulatory approval bodies. The condition calls for extra visits and follow ups to the regulatory bodies from the Sponsor/Investigators to push an application for a trial forward.

In some countries, independent ethics committees are not in line with regulatory requirements due to limited information about clinical trials that is conducted for regulatory submissions.

Institutional Review Boards/Ethics Committee (IRB/EC)

There is a continuing concern about local ethics committee capacity and their critical responsibilities to protect human subjects and provides oversight of studies. Despite many meetings and training to increase the capabilities of the IRB/EC members in Asian countries, the Sponsor’s still doubt that the approval by IRB/EC in Asia is not without its own challenges.

Clinical Trial Subjects

In terms of clinical trial subjects, it is difficult to enroll participants with the full understanding about the nature of the studies. There may be wide disparities in education and economic conditions that may jeopardize the rights of research participants. In phase I clinical trials, it is very hard to assess the willingness and motivation of the subjects to participate since there is no direct therapeutic benefit to them. Most of the subjects, however, take part for easy money despite the small amount of money provided.
This phenomenon does not only happen in Asia but in every part of the world. In some places, financial compensation for clinical research participation may exceed participants’ annual wages. Many phase I clinical trial volunteers are unlikely to have full time employment, thus do not have health insurance. Many of Asian countries do not have insurance companies that will cover clinical trials. This is one of the reasons why clinical trial budget is low. The lack of medical insurance for clinical trials may be judged as unethical.

Many subjects in phase I trials see their participation as a job. Subjects whose lives depend on trials often drop out of risky and unpleasant trials.

Phase I clinical trials are always problematic when dealing with subjects. However, the safety and well-being of the healthy individuals or patients must always be given top priority.

**FUTURE DIRECTIONS**

Given the above issues, we proposed multiple approaches to address the problems. The goal is for early clinical trials conducted in Asia to be proportional to the potential uses of the drugs after approval, resulting in safety problems to be identified from the earliest of drug development process. All of the stakeholders in clinical trials have to put in their effort to find solutions to the problems. In the future, it is essential to have hands on clinical trials even from the very beginning of the drug development on health problems that are priorities in Asian countries.

Conducting global early clinical trials would also mean globalizing quality in clinical trials. Industry sponsors and academia should work together to solve the ethical and scientific problems of phase I clinical trials. Continuing education and training are required to increase the quality of clinical trials. Not only do investigators and IRB members need to be specifically and continuously trained, but also clinical trial subjects. The trial subjects need to be given a thorough understanding about the nature of the study, so it is hoped that there will be no exploitation of vulnerable subjects. Rigorous training and capacity building of phase I research centers are required since many research centers have variable standards, specifically considering safety. Capacity building can benefit the community by strengthening local research capacity.

Improved collaboration among academic investigators in Asian countries would also increase the quality of multinational trials. Investigators in countries with lower experiences in clinical trials would benefit from trainings about design, conduct and ethical oversight of trials.

Regulatory bodies should work hard for the implementation of a comprehensive regulations in clinical trials and make control mechanism for adherence to the GCP and local regulations. It may also calls for harmonization of clinical research in Asian countries. It is hoped that Tripartite (Japan, Korea, China) collaboration will expand to other Asian countries in the near future.

**CONCLUSION**

Asia is still under-represented in the early phase clinical trials. International collaboration and capacity building can lead to solution of problems arising with the current status of first in human trials. Clinical trials stakeholders have to work hand in hand to address the challenges arising in conducting phase I clinical trials. Furthermore, we must ensure that everything is done for the benefit of the Asian populations.

**REFERENCES**


